(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 414 421 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90308784.9

(22) Date of filing: 09.08.90

(51) Int. Cl.5: C07D 491/10, C07D 498/10, A61K 31/335, A61K 31/42, //(C07D491/10,317:00,221:00), (C07D498/10,263:00,221:00)

(30) Priority: 10.08.89 HU 409589

(43) Date of publication of application: 27.02.91 Bulletin 91/09

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: RICHTER GEDEON VEGYESZETI GYAR R.T.
Gyömröi ut 19-21
H-1475 Budapest X(HU)

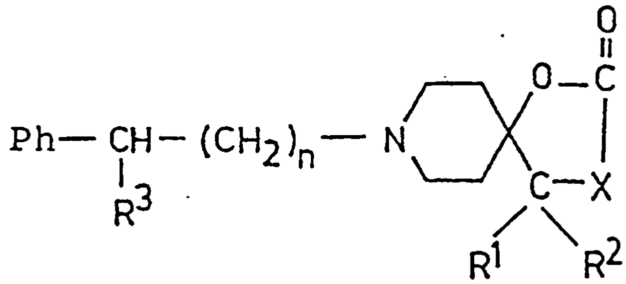
(72) Inventor: Toth, Edit
Szabolcska M. u. 17
H-1114 Budapest(HU)
Inventor: Torley, Jozsef
Katona J. u. 41
H-1137 Budapest(HU)
Inventor: Szporny, Laszlo, Dr.
Szabolcska M. u. 7
H-1114 Budapest(HU)
Inventor: Kiss, Bela
Gergely u. 48
H-1103 Budapest(HU)
Inventor: Karpati, Egon, Dr.
Mihalyfi E. u. 7/b
H-1025 Budapest(HU)
Inventor: Palosi, Eva, Dr.
Vend u. 21
H-1025 Budapest(HU)
Inventor: Groo, Dora, Dr.
Napraforgo u. 17
H-1021 Budapest(HU)
Inventor: Laszlovszky, Istvan, Dr.
Bartok B. u. 16
H-1111 Budapest(HU)
Inventor: Szombathelyi, Zsolt, Dr.
Kassak L. u. 9
H-1134 Budapest(HU)
Inventor: Sarkadi, Adam, Dr.
Thokoly ut 85
H-1146 Budapest(HU)
Inventor: Gere, Aniko
Egry J. u. 40
H-1111 Budapest(HU)
Inventor: Csomor, Katalin
Nyar u. 99
H-1045 Budapest(HU)
Inventor: Bodo, Mihaly, Dr.
Kis J. u. 47
H-1126 Budapest(HU)
Inventor: Laszy, Judit, Dr.
Beregszasz u. 40
H-1112 Budapest(HU)
Inventor: Szentirmay, Zsolt
Mosolygo A. u. 26/a
H-1158 Budapest(HU)

(74) Representative: Pett, Christopher Phineas et al
Frank B. Dehn & Co. European Patent Attorneys Imperial House 15-19 Kingsway
London WC2B 6UZ(GB)

(54) 1-Oxa-2-oxo-8-azaspiro[4,5] decane derivatives, processes for their preparation and pharmaceutical compositions thereof.

(57) The invention relates to 1-oxa-2-oxo-8-azasprio [4,5]decane derivatives of formula (I),

EP 0 414 421 A2



(I)

wherein
X represents an oxygen atom or an NR group,
wherein
R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl group, or a carbocyclic C_{6-10} aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;
R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1 and R^2 additionally represents a hydroxyl group and the other additionally represents a methyl group;
R^3 represents a hydrogen atom or a phenyl group optionally substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxyl group;
Ph represents a phenyl group unsubstituted or substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or trihalomethyl groups; and
n is 1, 2, 3;
and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof.

The invention further relates to pharmaceutical compositions containing these compounds and processes for their preparation.

The compounds of formula (I) possess calcium, uptake-inhibiting, antihypoxic and antianoxic properties and a low toxicity. Thus, they are useful for the treatment of brain damage of various origin.

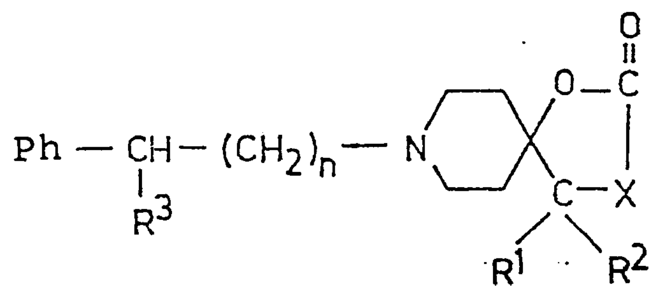
1-OXA-2-OXO-8-AZASPIRO[4, 5]DECANE DERIVATIVES, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS THEREOF

The invention relates to 1-oxa-2-oxo-8-azaspiro [4, 5]decane derivatives, processes for their preparation and pharmaceutical compositions thereof.

A number of therapeutically useful 1-oxa-2-oxo-3,8-diazaspiro[4, 5]decane derivatives have been described in the literature e.g. C.A. 71 , 91359d (1969); C.A. 78 , 719668t (1973); C.A. 78 , 23876q (1973); C.A. 81 , 33153c and 105368b (1974) ; C.A. 95 , 161765e (1981); as well as in the DE patent specifications Nos. 2,013,729, 2,013,668 and 2,163,000; in the Belgian patent specifications Nos. 775,984, 774,170, 786,631 and 825,444; in the British patent specification No. 1,100,281; in the published Dutch patent application No. 7,214,689 as well as in the United States patent specifications Nos. 3,555,033, 3,594,386, 4,244,961 and 4,255,432.

We have now developed a novel range of compounds based on this ring system but for which the substituents bound in the 4-position and optionally in the 3-position of the spirodecane skeleton are substantially different.

According to one aspect of the present invention, there are provided compounds of formula (I)



(I)

wherein

X represents an oxygen atom or a NR group, wherein

R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl group, or a carbocyclic C_{6-10} aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;

R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1 and R^2 additionally represents a hydroxyl group and the other additionally represents a methyl group;

R^3 represents a hydrogen atom or a phenyl group optionally substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxyl group;

Ph represents a phenyl group unsubstituted or substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or trihalomethyl groups; and

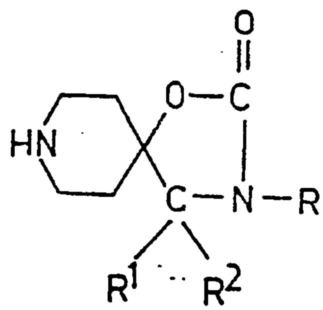
n is 1, 2, 3;

and all acid addition and guaternary ammonium salts thereof.

The compounds of the formula (I) may exist in various stereoisomeric forms such as geometrical isomers as well as racemates, individual optical isomers and their mixtures, all of which may also occur in the form of various solvates and hydrates. All these compounds and mixtures are within the scope of the present invention.

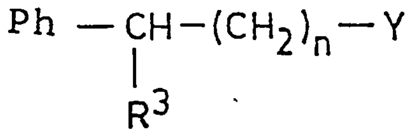
According to another aspect of the invention, there is provided a process for the preparation of compounds of the formula (I) and their acid addition and quaternary ammonium salts, which comprises

a) for the preparation of compounds of formula (I) wherein X is a group NR, reacting a 2-oxo-3,8-diazaspiro[4,5]decane derivative of formula (II),



(II)

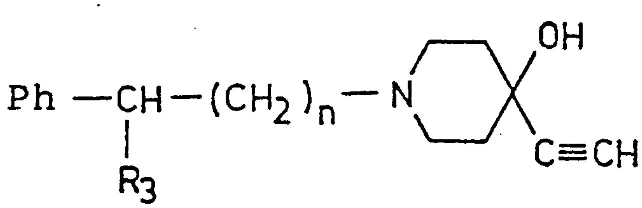
wherein R, R^1 and R^2 are as herein before defined with a phenylalkane derivative of formula (III),



(III)

wherein R^3, Ph and n are as herein before defined and Y represents a halogen atom or a C_{1-4} alkylsulfonyloxy or arylsulfonyloxy group; or

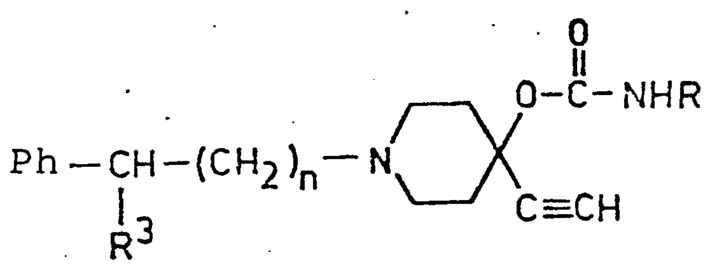
b) for the preparation of compounds of formula (I) wherein R^1 and R^2 together are a methylene group reacting a 4-ethynyl-4-hydroxypiperidine derivative of formula (IV),



(IV)

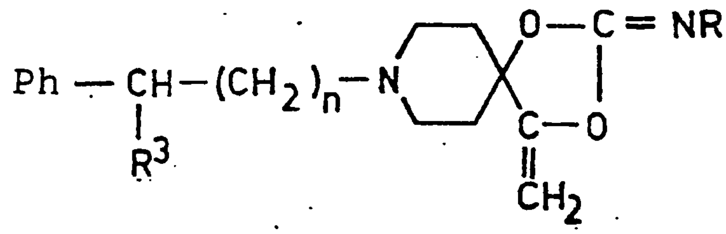
wherein R^3, Ph and n are as defined above with an isocyanate of formula R-NCO, wherein R is as defined above, and either

α) for compounds wherein X is an oxygen atom, cyclizing in an acidic medium the 4-carbamoyloxy-4-ethynylpiperdine derivative of the formula (V) as prepared above



(V)

wherein R, R^3 Ph and n are as defined above and reacting the resulting salt of formula (VI),



(VI)

wherein R, R^3 Ph and n are as defined above, with water;

or

β) for compounds wherein X is a group NR, cyclizing in a basic medium the compound of the formula (V) as defined and prepared above;

or

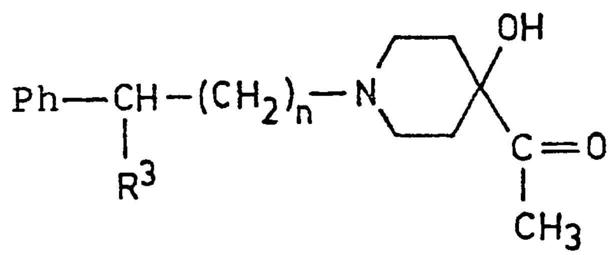
c) for the preparation of compounds of formula (I) as defined in process (b) (α) above, cyclizing in an acidic medium a 4-carbamoyloxy-4-ethynylpiperidine derivative of the formula (V) as defined above and reacting the obtained salt of formula (VI) as defined above with water;

or

d) for the preparation of compounds of formula (I) as defined in process (b) (β) above, cyclizing in the presence of a base a 4-carbamoyl-oxy-4-ethynylpiperidine derivative of formula (V) as defined above;

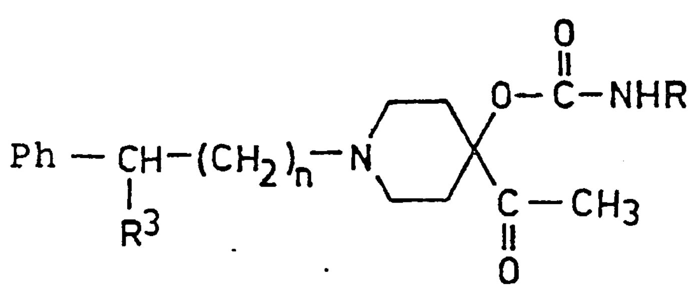
or

e) for the preparation of a compound of formula (I) wherein X is a group NR and one of R_1 and R_2 is a hydroxy group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypiperidine derivative of formula (VII),



(VII)

wherein R^3, Ph and n are as defined above, with an isocyanate of formula R-NCO wherein R is as defined above, and cyclizing the thus formed compound of formula (VIII)



(VIII)

wherein R, R^3 Ph and n are as defined above;

or

f) for the preparation of compounds of formula (I) as defined for process (e) above, cyclizing a 4-acetyl-4carbamoyloxypiperidine derivative of the formula (VIII) as defined above;

followed if desired or necessary,

by reacting a compound of formula (I) as prepared above wherein X is an oxygen atom and R^1 and R^2 together are a methylene group with an amine of formula $R\text{-}NH_2$ wherein R is as defined above, in order to prepare a compound of the formula (I), wherein X is a group NR and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group;

and/or if desired or necessary,
transforming a compound of the formula (I) as prepared above into another compound of the formula (I) as hereinbefore defined;
and/or if desired or necessary,
reacting a compound of formula (I) as prepared above with an acid to obtain the acid addition salt thereof and/or treating a salt of a compound of formula (I) as prepared above with a base to liberate the base form thereof and/or converting a thus prepared compound of the formula (I) into its quaternary ammonium salt.

In the process a) above, Y represents a leaving group, e.g. a mesyloxy or tosyloxy group, or a halogen atom, preferably chlorine or bromine. This reaction is preferably carried out in an inert organic solvent, and desirably in the presence of a base capable of binding the acid liberated in the reaction. Various solvents, such as aliphatic alkanols, e.g. ethanol, isopropanol, butanol; aromatic hydrocarbons, e.g. chlorobenzene, toluene; ethers, e.g. dibutyl ether or dioxane; tertiary aliphatic acid amides such as dimethylformamide or dimethylacatamide; ketones, e.g. acetone, methyl ethyl ketones or methyl isobutyl ketone or any mixtures of the above solvents may be used. As acid binding agents inorganic or tertiary organic bases, e.g. alkaline or earth alkaline metal carbonates or hydrogen carbonates as well as triethylamine, dimethylaniline or pyridine may be employed though an excess of the compound of formula (II) can also be used for the same purpose. This reaction may be carried out at a temperature between room temperatue and the boiling point of the reaction mixture, optionally in the presence of a catalyst. Suitable catalysts are e.g. the alkaline metal iodides. The reaction is preferably performed under an inert gas such as nitrogen or argon.

In the first step of process b) above, a 4-ethynyl-4-hydroxypiperidine derivative of the formula (IV) may be brought into reaction with an isocyanate of the formula R-NCO in a manner known per se [Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)] to give a 4-carbamoyloxy-4-ethynyl-piperidine derivative of the formula (V). For preparing compounds of the formula (I) wherein X is an oxygen atom, the compound of the formula (V) is cyclized in an acidic medium according to step α), then the thus-formed 2-imino-1,3-dioxolane derivative of the formula (VI) obtained as a salt is reacted with water; for preparing compounds of the formula (I) where X is a >NR group, the compound of formula (V) is cyclized in a basic medium according to step β).

The cyclization of step α) may be carried out in an inert organic solvent (i.e. in a solvent which is inert under the reaction conditions), in the presence of a suitable acid, preferably in the presence of a dry hydrogen halide. Aliphatic or alicyclic ethers such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tetrahydrofuran or dioxane as well as lower aliphatic carboxylic acids, e.g. acetic or propionic acid, may be employed.

As a hydrogen halide hydrogen chloride, bromide, iodide or fluoride, preferably hydrogen chloride or bromide, may be used. Following the reaction with water, the 1-oxa-2-oxo-8-aza-spiro[4,5]decane derivative of the formula (I) is obtained as an acid addition salt from which, if desired, the base can be liberated in a manner known per se .

The cyclization of step β) may be realized in the presence of a base. Alkaline metal acetates, carbonates, alkoxides, hydroxides and/or tertiary organic bases, e.g. pyridine, tripropylamine or picoline, may be used as basic catalysts in the cyclization; the organic bases may also serve as solvents for the reaction. Further suitable solvents are aliphatic alcohols, e.g. methanol, ethanol, propanol or butanol; aliphatic, alicyclic or aromatic hydrocarbons, e .g. hexane, cyclohexane, benzene, toluene or xylene; acid amides, e.g. dimethylformamide or N-methyl-2-pyrrolidone; ethers such as dibutyl ether or dioxane; nitriles such as acetonitrile; sulfoxides, e.g. dimethylsulfoxide; etc. and any mixture of the above solvents. The reaction may also be carried out without any solvent, e.g. in a molten state. In order to accelerate the cyclization the temperature may be suitably increased. The reaction is preferably accomplished between 40 °C and the boiling point of the reaction mixture. It is preferable to work under an inert gas such as argon or nitrogen. According to a preferred embodiment of the present invention the 4-carbamoyloxy4-ethynyl-piperidine derivative of the formula (V), formed in the reaction of the 4-ethynyl-4-hydroxypiperidine derivative of the formula (IV) with the isocyanate of the formula R-NCO, is directly cyclized in the same reaction mixture, in the presence of a suitable base, ie. the derivative of formula (V) is not isolated prior to cyclization.

In the processes c) and d) above the procedures as discussed for steps α) and β) above may be followed.

In the process e) above, a 4-acetyl-4-hydroxypiperidine derivative of the formula (VII) is reacted with an isocyanate of the formula R-NCO and the obtained 4-acetyl-4-carbamoyloxypiperidine derivative of the formula (VIII) is cyclized. The condensation reaction according to the first step may be realised in a manner known per se [Houben-Weyl: Methoden der Organischen Chemie Vol. VIII/3, pages 137 to 147 (1952)]. The

obtained 4-acetyl-4-carbamoyloxypiperidine derivative of the formula (VIII) is preferably cyclized in the presence of a base. The cyclization may be carried out under the same reaction conditions as described for step β) of process b) above. Alternatively, according to a preferred embodiment of process (b) (β) of this invention, the 4-acetyl-4-carbamoyloxypiperidine derivative of the formula (VIII), created in the reaction of the 4-acetyl-4-hydroxypiperidine derivative of the formula (VII) with the isocyanate of formula R-NCO, may be cyclized directly in the same reaction mixture, and in the presence of a suitable base i.e. the derivative of formula (VIII) is not isolated from its reaction mixture before its cyclization.

For process f) above, the procedure in the second step of process e) above may be followed.

If desired or necessary, the compounds of formula (I) as prepared in any one of the processes a) to f) above may be transformed into other compounds within the scope of the formula (I) in a manner known per se .

Thus, on reacting a compound of the formula (I) as prepared above wherein X is an oxygen atom and R^1 together with R^2 are a methylene group with an amine of formula R-NH_2 wherein R is as defined above, a compound of formula (I) may be prepared wherein X is a >NR group and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group. This reaction may be carried out in a suitable solvent or without any solvent. Convenient solvents are e.g. aliphatic, alicyclic or araliphatic alcohols such as ethanol, butanol, cyclohexanol, benzyl alcohol; aliphatic or aromatic hydrocarbons such as hexane, heptane, xylene, chlorobenzene or nitrobenzene; ethers, e.g. dioxane; ketones, e.g. di-n-butyl ketone; tertiary organic bases, e.g. picoline, triethylamine or pyridine. An excess of the R-NH_2 amine may also serve as a solvent for this reaction. This procedure may be carried out at a temperature between room temperature and the boiling point of the reaction mixture, preferably under an inert gas, e.g. argon or nitrogen.

If desired or necessary, a compound of the formula (I) wherein R_1 and R_2 are a hydroxyl and a methyl group may be dehydrated into a compound of formula (I) wherein R^1 and R^2 together are a methylene group. The dehydration may be achieved under normal or reduced pressure using well-known procedures. Isocyanates, aliphatic carboxylic acids, aliphatic or aromatic carboxylic acid anhydrides, Lewis acids, sulfuric acid or aromatic sulfonic acids may be employed for the dehydration. This reaction is preferably performed in an organic solvent. Suitable solvents are e.g. aromatic hydrocarbons such as benzene, toluene or xylene; ethers such as dioxane, di-n- butyl ether; or aliphatic carboxylic acids such as acetic acid. optionally, the water formed in the reaction may be removed by azeotropic distillation.

If desired or necessary, the reverse reaction to the dehydration process described above may be carried out by adding water to a compound of formula (I) wherein R^1 and R^2 together are a methylene group to give a compound of the formula (I) wherein R_1 and R_2 are a hydroxyl and a methyl group. This hydration reaction may be accomplished in an aqueous medium, in the presence of mineral and/or organic acids. As acids e .g. hydrogen halides, sulfuric, phosphoric, formic acid, aromatic sulfonic acids, oxalic or trifluoroacetic acid and the like may be employed. This reaction may be carried out between 5 °C and the boiling point of the reaction mixture.

The compounds of the formula (I) may be converted into their acid addition salts or quaternary ammonium salts by using methods known per se . For the preparation of acid addition salts, inorganic or organic acids such as hydrogen halides, e.g. hydrochloric acid and hydrobromic acid, sulfuric acid, phosphoric acids as well as formic, acetic, propionic, oxalic, glycolic, maleic, fumaric, succinic, tartaric, ascorbinic, citric, malic, salicylic, lactic, benzoic, cinnamic, aspartic, glutamic, N-acetyl-aspartic or N-acetylglutamic acid as well as alkanesulfonic acids such as methanesulfonic acid or arenesulfonic acids, e.g. p-toluenesulfonic acid and the like may be used.

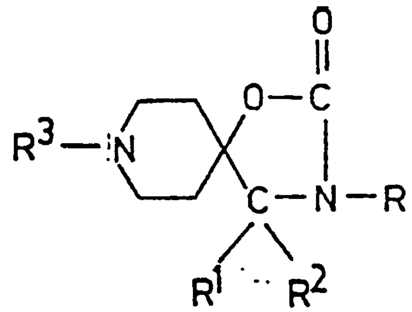
Salt formation may be carried out e.g. in such a way that the relevant acid is added to the solution of the compound of formula (I) in an inert solvent, e.g. ethanol, and the salt formed is precipitated by adding preferably a water-immiscible organic solvent, e.g. ethyl ether. For the preparation of quaternary ammonium salts a lower alkyl, alkenyl or benzyl halide or an alkyl sulfate may preferably be employed. The quaternization may be performed in an organic solvent such as acetone, acetonitrile, ethanol or their mixtures, at a temperature in the range from room temperature up to the boiling point of the solvent. The acid addition or quaternary ammonium salt obtained may be isolated e.g. by filtration and, when necessary, purified by recrystallization.

Conversely, the corresponding bases can be liberated from their salts by an alkaline treatment.

The compounds of formula (III) may be prepared according to e.g. Collection Czechoslov. Chem. Commun. 38 , 3879 (1973); as well as Chim. Ther. 3 , 185 (1969).

The preparation of compounds of formula (II) is described in our European patent application of even date, claiming priority from our Hungarian patent application No. 4092/89.

This preparation comprises the reduction of compounds of formula (X)

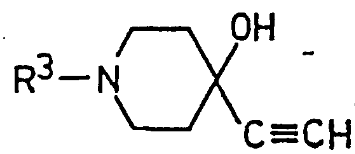


(X)

wherein R_1 and R_2 are as defined above and R^3 represents a benzyl, (C_{1-4} alkoxy)carbonyl, phenoxycarbonyl, formyl, piperidin-1-yl-carbonyl, morpholin-4-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-(2-hydroxyethyl)piperazin-1-ylcarbonyl, 2-chloro-3-nicotinoylcarbamoyl or C_{1-6}alkylcarbamoyl group.

The compounds of formula (X) may be prepared as also described in the above-mentioned application by:

(i) reacting a compound of formula (XI)



(XI)

wherein R^3 is as defined above with an isocyanate of formula RNCO wherein R is as hereinbefore defined followed by cyclizing the resulting compound in a basic medium in order to prepare compounds of formula (X) wherein R_1 and R_2 together represent a methylene group;

and, if necessary;

(ii) hydrogenating a compound as prepared in reaction (a) above in order to obtain compounds of formula (X) wherein one of R_1 and R_2 is a hydroxy group and the other a methylene group.

Compounds of formula (XI) may be prepared by a procedure analogous to the preparation of compounds of formula (IV) as described below.

The substances of formula (IV) may be synthesized e.g. by the ethynylation reaction of suitably substituted 4-piperidone derivatives as described in e.g. Hungarian patent specification No. 166,769 or in Farmaco (Pavia) Ed. Sci. 12 , 34 (1957).

The 4-acetyl-4-hydroxypiperidine derivatives of formula (VII) may be prepared by e.g. hydrating the corresponding 4-ethynyl-4-hydroxypiperidine derivatives of formula (IV) as defined above, as e.g. Houben-Weyl: Methoden der Organischen Chemie Vol. VII/2 a, pages 826 to 835 (1973) or by the alkaline treatment of the corresponding 1,3-dioxa--2-oxo-4-methylene-8-azaspiro[4,5]decane derivatives of formula (I).

The compounds of formulae (IV), (V), (VII) and (VIII) as defined above are all novel compounds which are valuable intermediates in the synthesis of the compounds according to the present invention, and, in addition, they are also biologically active.

The compounds of formula (I) as well as their stereoisomers and salts exhibit valuable pharmacological properties such as calcium uptake-inhibiting, antihypoxic and antianoxic effects. Thus they are useful for the systemic (i.e. oral, rectal or parenteral) treatment of warm-blooded mammals (including man). They may be favourably employed for the prevention or therapeutic treatment of hypoxic brain damages of various origin such as senile dementia, Alzheimer's disease, ischemic lesions, dis turbances of the cognitive function, multi-infarctual dementia, hypoxia following atheroschlerosis and the like.

The calcium uptake-inhibiting action of the compounds of formula (I) was studied on a rat brain synaptosomal preparation by using the method of P. H. Wu et al. [J. Neurochem. 39 , 700 (1982)].

Wistar rats weighing 180 to 200 g were decapitated, their brains were collected in an ice-cold physiological saline solution, the cortex was removed and purified from the white substance. The tissue was homogenized in 10 volumes of 0.32 M sucrose solution by using a glass-teflon potter. After centrifuging the homogenate at a rate of 1000 x g at 4 °C for 10 minutes, the supernatant was further centrifuged at 10000 xg for 20 minutes. The sediment was taken up in a 0.32 M sucrose solution in such a way that the protein content of the preparation was adjusted to 20 mg/ml.

The medium (containing 112 mM of sodium chloride, 5 mM of potassium chloride, 1.3 mM of magnesium chloride, 1.2 mM of sodium dihydrogen phosphate, 1.2 mM of calcium chloride, 10 mM of glucose, 20 mM of TRIS buffer) used for the incubation was saturated with carbogen, consisting of 95% by volume of oxygen and 5% by volume of carbon dioxide, up to a pH of 7.4. After adding the test substances to the medium, the synaptosomal preparation was added in an amount corresponding to 1 mg of protein. The incubation was carried out in a final volume of 1 ml. The samples were pre-incubated at 34 °C for 20 minutes. The calcium uptake was begun by using a $^{45}CaCl_2$ solution of 75 nCi activity. Potassium chloride used for investigating the potassium-induced ^{45}Ca uptake was employed in 60 mM concentration whereas sodium chloride was added in the same concentration to the control samples. The incubation lasted 20 seconds. The reaction was stopped by 5 ml of a stopping solution containing 120 mM of sodium chloride, 5 mM of potassium chloride, 5 mM of EGTA and 20 mM of TRIS at pH 74. The samples were filtered through a Whatman GF/C filter paper and twice washed with 5 ml of a washing solution each, containing 132 mM of sodium chloride, 5 mM of potassium chloride, 1.3 mM of magnesium chloride, 1.2 mM of calcium chloride and 20 mM of TRIS at pH 7.4. (Abbreviations used above: TRIS means tris(hydroxymethyl)aminomethane; EGTA means ethylene glycol bis(β-aminoethyl) ether-N,N,N′,N′-tetraacetic acid).

The filter papers were put into glass cuvets, 10 ml of a scintillation cocktail each were added, then the radioactivity of the samples was measured in an 1219 Rackbeta (LKB Wallace) liquid scintillation spectrophotometer.

The IC_{50} values obtained by examination of the concentration/effect correlations are shown in Table I. IC_{50} value means the molar concentration of the test compounds which causes 50% inhibition of the stimulated ^{45}Ca uptake.

Table I

Compound No.	IC_{50} µM
1	5.8
2	5.9
3	2.1
4	5.3
5	6.1

Numbers for the chemical names and abbreviations used in the Tables:

1 1-Oxa-2-oxo-3-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

2 1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

3 1-Oxa-2-oxo-3-phenyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

4 1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

5 1-Oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride

6 1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane

7 1-Oxa-2-oxo-3-propyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane

8 1-Oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4fluorophenyl)ethyl]3,8-diazaspiro[4,5]decane

9 1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane.

Abbreviations:

n: number of animals

p.o.: oral administration

iv.: intravenous injection

S.E.: standard error

The antihypoxic effect was studied by using two methods. According to the method of C. Caillard et al. [Life Sci. 16 , 1607 (1975)] the asphyxial action was determined after starvation for 16 hours on CFLP mice of both sexes weighing 24 to 26 g. Each animal was placed in a separate well-closed glass cylinder. The time elasped between the closing of the cylinder until the cessation of the last visible respiratory movement was registered as survival time. Animals surviving longer by 30% than the average survival time of the control group, were considered to be protected. The test substances were administered in an oral dose of 50 mg/kg 60 minutes before starting the test. The results are summarized in Table II.

Table II

Compound No.	Protected animals %	n
6	60	10
7	40	10
8	60	10
9	60	10

The average survival time of the control group was 23.5 ± 2.51 sec (X±S.E.)

The potassium cyanide test method was used for determination of the protective effect against the histotoxic hypoxia. A hypoxia of this type can be developed by a rapid intravenous injection of 5.0 mg/kg of potassium cyanide inducing abdominal contractions within and clonic convulsions of the animals and leading to death of the animals within 2 minutes.

Male Hannover-Wistar rats weighing 160 to 170 g were used in this experiment. Animals surviving longer by 30% than the average survival time of the control group were considered to be protected. The test substances were orally administered in various doses 60 minutes before starting the test. The ED_{50} values, i.e. the dose protecting 50% of the treated animals from the hypoxia, were calculated from the percentage of the protected animals relating to various doses (i.e. from the dose-response curve) by using probit analysis. The results are summarized in Table III.

Table III

Compound No.	ED_{50} p.o. mg/kg
1	40.9
2	39.9
4	37.9

The compounds according to the invention showed a strong calcium-antagonizing and antihypoxic activity and had a low toxicity. Their oral LD_{50} values (i.e. the dose causing death of 50% of the animals) were found to be higher than 1000 mg/kg; thus, their therapeutic indices are favourable.

The present invention also relates to the use of a compound of formula (I) as hereinbefore defined in the treatment of antihypoxic and antianoxic damage of mammals. They are also useful in inhibiting calcium-uptake in mammals.

The compounds according to the invention can be formulated into pharmaceutical compositions in a known manner. The pharmaceutical compositions may be administered in oral, rectal and/or parenteral route. For oral administrastion, the composition may be formulated e.g. as a tablet, dragée or capsule. In order to prepare oral compositions, e.g. lactose or starch may be used as carriers. Gelatine, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or starch gum are suitable binding or granulating agents. As disintegrating agents, potato starch or microcrystalline cellulose may be added though ultraamylopectin or formaldehyde-casein and the like are also useful. Talc, colloidal silicic acid, stearin, calcium or magnesium stearate and the like are suitable anti-adhesive and sliding agents. The liquid oral compositions of the invention may be prepared in the form of e.g. a suspension, syrup or elixir which may contain water, glycols, oils, alcohols as well as colouring and flavouring additives.

Tablets may be prepared e.g. by compression following wet granulation. The mixture of the active ingredient with the carriers and optionally with a part of the disintegrating additive is granulated with an aqueous, alcoholic or aqueous-alcoholic solution of the binding agents, then the granulate is dried. Subsequently, after mixing the other disintegrating, sliding and anti-adhesive additives to the dried granulate, the mixture is compressed into tablets. If desired, the tablets may be provided with a groove in order to facilitate their administration. Tablets may also directly be prepared from a mixture containing the

active ingredient and suitable additives. The tablets may optionally be converted to dragées by employing the commonly used pharmaceutical additives, e.g. protective, flavouring or colouring agents such as sugar, cellulose derivatives (methyl- or ethyl-cellulose, sodium carboxymethylcellulose and the like), polyvinylpyrrolidone, calcium phosphate, calcium carbonate, food dyes, dyeing lacquers, aromatizing agents, iron oxide pigments and the like. Capsulated compositions may be prepared by filling a mixture of the active ingredient with the additives into capsules.

For rectal administration, the composition of the invention may be formulated as a suppository containing a carrier mass, the so-called "adeps pro suppositorio", in addition to the active ingredient. As carriers, vegetable fats such as hardened vegetable oils, or triglycerides of C_{12-18} fatty acids (preferably the carriers bearing the trade name Witepsol) may be used. The active ingredient is uniformly distributed in the molten carrier mass, then suppositories are prepared by moulding.

For parenteral administration, the composition of the invention may be formulated as an injectable solution. For preparing these injectable solutions, the active ingredients are dissolved in distilled water and/or various organic solvents, e.g. glycol ethers, if desired, in the presence of solubilizing agents such as polyoxyethylene sorbitan monolaurate or monooleate or monostearate (Tween 20, Tween 60, Tween 80), respectively. The injectable solution may further contain various additives (auxiliary agents), e.g. preservatives such as ethylenediamine tetraacetate as well as p-modifying and buffering substances or, if desired, a local anaesthetic agent such as lidocaine. Before filling into the ampouls, the injectable solution containing the composition of the invention is filtered and after filling in, it is subjected to sterilization.

On using the pharmaceutical composition of the invention, the patient is treated with a dose sufficient to ensure the desired effect. This dose depends upon several factors like the severity of the disease, the body-weight of the patient and the route of administration. The dose to be used in every case is to be defined by the physician.

According to a yet further feature of this invention, the compounds of the invention as defined herein may be used in the manufacture of a medicament for the treatment of hypoxic brain damages of various origin such as the senile dementia, Alzheimer's disease hypoxia following atherosclerosis, multi-infarctual dementia and disturbances of the cognitive function. This treatment comprises administering a therapeutically effective amount of an active ingredient of the formula (I) or a pharmaceutically acceptable acid addition salt thereof to the patient.

The invention is illustrated by way of the following non-limiting Preparations and Examples.

Preparation 1

4-ethynyl-4-hydroxy-1[4,4-bis(4-5-fluorophenyl)butyl]piperidine hydrochloride

Acetylene is introduced into a solution containing 38.4 g of potassium tert-butoxide in 250 ml of tetrahydrofuran at a temperature between 0 °C and -5 °C under stirring for 30 minutes, then 78.0 g of 1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidone dissolved in 200 ml of tetrahydrofuran are dropwise added and acetylene is introduced for an hour thereafter. Then the reaction mixture is cooled to -10 °C and saturated aqueous ammonium chloride solution is added under nitrogen. After evaporating off the tetrahydrofuran under reduced pressure, the residue is extracted with benzene. The benzene solution is washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. After taking up the residue in acetone, the hydrochloride is precipitated by adding hydrogen chloride in diisopropyl ether solution. The title hydrochloride is obtained in 91.0% yield, m.p.: 166-168 °C.
Analysis for the base:

Analysis for the base:				
Calculated for $C_{23}H_{25}F_2NO$				
	C 74.77;	H 6.82;	F 10.28;	N 3.79%;
found:	C 74.85;	H 6.66;	F 10.15;	N 4.00%.

Preparation 2

4-butylcarbamoyloxy-4-ethynyl-1-[4,4-bis(4-fluorophenyl)butyl]piperidine hydrochloride

6.4 ml of butyl isocyanate dissolved in 19 ml of benzene are dropwise added to a mixture of 18.5 g of 4-ethynyl-4-hydroxy-1-[4,4-bis(4-fluorophenyl)butyl]-piperidine, 0.35 g of anhydrous powdered potassium carbonate and 74 ml of benzene in a nitrogen atmosphere under reflux and stirring. The mixture is refluxed for an hour thereafter, then cooled down and water is added. After separating the phases the benzene solution is washed with water to neutral, dried over anhydrous magnesium sulfate, the solution is filtered through a silica gel column and evaporated under reduced pressure. After taking up the residue in diisopropyl ether, the hydrochloride salt is precipitated by adding hydrogen chloride in diisopropyl ether solution. The title hydrochloride is obtained in 87.5% yield, m.p.: 84-89 °C.

Analysis of the base:				
Calculated for $C_{28}H_{34}F_2NO_2$				
	C 71.77;	H 7.31;	F 8.11;	N 5.98%.
found:	C 71.88;	H 7.50;	F 8.28;	N 5.83%.

Preparation 3

4-acetyl-4-hydroxy-1-[4,4-bis(4-fluorophenyl)butyl]piperidine hydrochloride

A solution of 1,3-dioxa-2-oxo-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-8-azaspiro[4,5]decane (Example 14 below) in 100 ml of a 2.8 molar sodium hydroxide solution is stirred at 80 to 90 °C under argon. After cooling down the reaction mixture is extracted with benzene, the benzene layer is washed with water to neutral, dried over anhydrous sodium sulfate, then the solvent is distilled off under reduced pressure. The evaporation residue is dissolved in diisopropyl ether and the hydrochloride is precipitated by adding hydrogen chloride in diisopropyl ether solution. The title hydrochloride is obtained in 61% yield, m.p. : 62-67 °C.

Analysis of the base:				
Calculated for $C_{23}H_{27}F_2NO_2$				
	C 71.29;	H 7.02;	F 9.81;	N 3.61%;
found:	C 71.27;	H 7.18;	F 9.63;	N 3.80%.

Preparation 4

4-methylene-2-oxa-3-n-propyl-1-oxa-3,8 diazaspiro [4,5] decane

(a) 8-benzyl-3-n-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane

21.5 g of 1-benzyl-4-ethynyl-4-hydroxypiperidine are boiled under reflux with 12.9 g of n-butyl isocyanate in the presence of 0.4 g of anhydrous potassium acetate in 66 ml of 2-picoline under nitrogen for 6 hours. After evaporating 2-picoline under reduced pressure and dissolving the residue in benzene, the

organic solution is washed with water and dried over anhydrous magnesium sulfate. After filtration on an aluminum oxide layer the benzene solution is evaporated under reduced pressure. The crude product obtained is recrystallized from n-heptane to give the pure title substance in 78.5% yield, m.p. : 57-58 °C.

Analysis:			
Calculated for $C_{19}H_{26}N_2O_2$			
	C 72.58;	H 8.33;	N 8.91%;
found:	C 72.55;	H 8.53;	N 9.06%.

Using the appropriate starting materials the following compounds may be prepared in an analogous manner; 8-Formyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 171-172 °C;
8-Benzyloxycarbonyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 145-146 °C;
4-Methylene-2-oxo-3-phenoxycarbonyl-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 208-210 °C;
8-Benzyl-3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 128-130 °C (the hydrogen fumarate salt melts at 207-208 °C);
8-Benzyl-3-ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 103-104 °C (hydrogen maleate salt m.p. : 184-186 °C);
8-Benzyl-3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-di-azaspiro[4,5]decane, m.p. : 116-117 (dihydrogen citrate salt m.p. : 132-133 °C);
8-Benzyl-4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 134-135 °C;
8-Benzyl-3-isopropyl-4-methylene-2-oxo-1-oxa3,8-diaza spiro[4,5]decane, m.p. : 96-97 °C;
8-Benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrogen maleate, m.p. : 210-211 °C;
8-Benzyl-4-methylene-2-oxo-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane dihydrogen citrate, m.p. : 168-171 °C;

(b) <u>3-tert-butyl-4-methylene-2-oxo-8-phenoxy carbonyl-1-oxa-3,8-diazaspiro[4,5]decane</u>

A solution of 3.6 g of phenyl chloroformate in 5 ml of methylene chloride are dropped into a solution of 6.3 g of 8-benzyl-3-tert-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane in 30 ml of methylene chloride under argon at 0°C while stirring, then the reaction mixture is stirred at room temperature for one additional hour. After termination of the reaction the mixture is diluted with 35 ml of methylene chloride, extracted with 4 N sodium hydroxide solution and washed to neutral with water. After drying over anhydrous magnesium sulfate the solvent is evaporated under reduced pressure. After adding n-hexane to the residue the solid precipitate is filtered off and recrystallized from isopropanol to obtain the title substance in 82% yield, m.p. : 125-126 °C.

Analysis:			
Calculated for $C_{19}H_{24}N_2O_4$			
	C 66.26;	H 7.02;	N 8.13%;
found:	C 66.33;	H 7.10;	N 8.10%.

Using the appropriate starting materials the following compounds may be prepared in an analogous manner.
3-Benzyl-8-benzyloxycarbonyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
8-benzyloxycarbonyl-3-butyl-4-methylene-2-oxo-1-oxa-3,8-diaza spiro[4,5]decane, m.p. : 47-48 °C;
8-ethoxycarbonyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 121-122 °C;
3-(3,4-dichlorophenyl)-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 220-222 °C;
3-methyl-4-methylene-2-oxo-8-phenoxycarbonyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 118-119 °C; and

4-methylene-2-oxo-8-phenoxycarbonyl-3-propyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 96-98 °C;

(c) 4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro[4,5]decane

A suspension containing 0.5 g of 10% by weight palladium-on-carcoal catalyst in 5 ml of water is added to the solution of 5.0 g of 8-benzyloxycarbonyl-4-methylene-2-oxo-3-n-propyl-1-oxa-3,8-diazaspiro[4,5]-decane in 45 ml of methanol at 0 °C under argon while stirring. To this mixture 1 ml of 45.8% aqueous hydrazine solution is introduced and the reaction mixture is refluxed for 10 to 15 minutes. After cooling down to room temperature and filtering off the catalyst the solvent is evaporated under reduced pressure and the crude evaporation residue is recrystallized from benzene to give the title compound in 95% yield, m.p.: 96-97 °C.

Using the appropriate starting materials the following compounds may be prepared in an analogous manner;
3-Ethyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 106-108 °C;
3-isopropyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 151-152 °C;
4-methylene-3-(1-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 208-209 °C;
3-butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
4-methylene-2-oxo-3-phenyl-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 185-186 °C;
3-tert-Butyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 138-139 °C;
3-heptyl-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 139-140 °C;
3-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-4-methyl-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 190-191 °C;
3-benzyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p.: 77-79 °C; 3-heptyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
3-decyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, oil;
3-cyclohexyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 141-142 °C;
3-[2-(3,4-dimethoxyphenyl)ethyl]-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane, m.p. : 107-109 °C.

Preparation 5

3,4-dimethyl-4-hydroxy-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane hydrochloride

A solution of 5.44 g of 8-benzyl-3-methyl-4-methylene-2-oxo-1-oxa-3,8-diazaspiro[4,5]decane (from Preparation 4(a)) in 40 ml of N hydrochloric acid is hydrogenated in the presence of 5.4 g of palladium-on-charcoal catalyst until the theoretical amount of hydrogen is consumed. After filtering off the catalyst the filtrate is evaporated to a volume of about 10 ml under reduced pressure and 40 ml of acetone are added. The crystalline precipitate is filtered off and dried to obtain the title compound in 87% yield, m.p. : 272-274 °C.

Analysis of the base:			
Calculated for $C_9H_{16}N_2O_3$			
	C 53.98;	H 8.05;	N 13.99%;
found:	C 54.16;	H 8.15;	N 14.20%.

Example 1

1-oxa-2-oxo-3-propyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

A mixture containing 8.4 g of 1-oxa-2-oxo-3-propyl-4-methylene-3,8-diazaspiro[4,5]decane, 22.4 g of

4,4-bis(4-fluorophenyl)butyl chloride, 16.6 g of anhydrous potassium carbonate and 0.3 g of potassium iodide in 90 ml of methyl isobutyl ketone is boiled under reflux and stirring for 8 hours, then the solvent is distilled off under reduced pressure. After adding benzene and water to the residue, the organic phase is separated, washed with water to neutral, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product obtained is purified by chromatography on a silica gel column by using ethyl acetate for elution. The eluates are combined, evaporated and the residue is recrystallized from diisopropyl ether to give the title compound in 89% yield, m.p. : 107-108 °C.

Analysis:				
Calculated for $C_{27}H_{32}F_2N_2O_2$				
	C 71.34;	H 7.10;	F 8.36;	N 6.16%;
found:	C 71.50;	H 7.23;	F 8.28;	N 6.07%.

Example 2

1-oxa-2-oxo-3-benzyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4.5]decane

A mixture containing 10.3 g of 1-oxa-2-oxo-3-benzyl-4-methylene-3,8-diazaspiro[4,5]decane, 16.2 g of 2-(4-fluorophenyl)ethyl bromide and 11.2 ml of triethylamine in 100 ml of methyl isobutyl ketone is refluxed under argon while stirring for 2.5 hours. After cooling down and adding water to the reaction mixture, the organic phase is separated, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue is recrystallized under clarifying by activated carbon from hexane and then from diisopropyl ether to obtain the title compound in 31,8% yield, m.p.: 100-101 °C.

Analysis:				
Calculated for $C_{23}H_{25}FN_2O_2$				
	C 72.61;	H 6.62;	F 4.99;	N 7.36%;
found:	C 72.8;	H 6.54;	F 5.22;	N 7.53%.

Example 3

1-oxa-2-oxo-3-ethyl-4-methylene-8-(3,3-diphenylpropyl)-3,8-diazaspiro[4,5]decane hydrogen maleate

A mixture containing 7.9 g of 1-oxa-2-oxo-3-ethyl-4-methylene-3,8-diazaspiro[4,5]decane, 26 g of 3,3-diphenyl-1-tosyloxypropane and 7.4 g of anhydrous sodium carbonate in 100 ml of methyl isopropyl ketone is refluxed under nitrogen while stirring for 5 hours. After evaporating the reaction mixture under reduced pressure, water is added to the residue and extracted with chloroform. The organic phase is washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product is dissolved in acetone and the title salt is precipitated by adding an ethereal solution of maleic acid, m.p. : 168-170 °C.

The base can be liberated from the above salt by adding aqueous sodium hydroxide solution.

Analysis of the base:			
Calculated for $C_{25}H_{30}N_2O_2$			
	C 76.89;	H 7.74;	N 7.17%;
found:	C 76.95;	H 7.89;	N 7.24%.

Example 4

1-oxa-2-oxo-3-decyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride

5.5 g of 1-oxa-2-oxo-3-decyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane are dissolved in 11 ml of formic acid and after dropping 100 ml of a 3 mol/litre hydrochloric acid to the solution under stirring, the reaction mixture is stirred for additional minutes. The crystals precipitated are filtered, washed with water and dried to give the title hydrochloride in 97.2% yield; m.p. : 109-111 °C. The base is liberated by adding aqueous sodium carbonate solution to the hydrochloride, extracted into chloroform, the organic phase is washed with water to neutral, dried over anhydrous sodium sulfate and evaporated under reduced pressure. After recrystallization from diisopropyl ether the base melts at 89-90 °C.

Analysis:				
Calculated for $C_{34}H_{48}F_2N_2O_3$				
	C 71.54;	H 8.48;	F 6.66;	N 4.91%;
found:	C 71.54;	H 8.31;	F 6.73;	N 4.99%.

Example 5

1-oxa-2-oxo-3-cyclohexyl-1-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane

A mixture containing 8.14 g of 1-oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-chlorophenyl)-ethyl]-3,8-diazaspiro[4,5]decane and 0.8 g of p-toluenesulfonic acid monohydrate in 100 ml of xylene is boiled under stirring while the water formed in the reaction is azeotropically distilled out. The reaction is followed by using thin-layer chromatography. After termination of the reaction the mixture is cooled down, made alkaline by adding 5% by weight aqueous sodium hydroxide solution, then the organic phase is washed with water to neutral, dried over anhydrous sodium sulfate and evaporated under reduced pressure. After recrystallizing the crude product from ethanol the pure title product is obtained in 92.4% yield, m.p. : 134-135 °C.

Analysis:				
Calculated for $C_{22}H_{29}ClN_2O_2$				
	C 67.93;	H 7.52;	Cl 9.12;	N 7.20%;
found:	C 67.88;	H 7.65;	Cl 9.25;	N 7.11%.

Example 6

1-oxa-2-oxo-3-methyl-4-methylene-8-(3-phenylpropyl)-3,8-diazaspiro[4.5]decane

A solution of 7.5 g of 4-ethynyl-4-methylcarbamoyl-oxy-1-(3-phenylpropyl)piperidine in 100 ml of an ethanolic sodium ethoxide solution of 0.09 mol/litre concentration is refluxed under argon for 3 to 4 hours. After cooling down and adding aqueous ammonium chloride solution to the reaction mixture, the major part of alcohol is distilled off under reduced pressure. The residue is diluted with water and extracted with benzene. The benzene phase is washed with water to neutral, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. After recrystallizing the residue from hexane, the title compound is obtained in 68% yield, m.p.: 35-36 °C.

Analysis:			
Calculated for $C_{18}H_{24}N_2O_2$			
	C 71.97;	H 8.05;	N 9.33%;
found:	C 71.88;	H 8.19;	N 9.52%.

Example 7

1-oxa-2-oxo-4-methylene-3-phenyl-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane

A mixture containing 6.2 g of 4-acetyl-4-hydroxy-1-(2-phenylethyl)-piperidine, 2 ml of triethylamine and 11 ml of phenylisocyanate in 20 ml of xylene is refluxed under argon for 6 hours. After cooling down and diluting with xylene the reaction mixture is filtered and the filtrate is evaporated under reduced pressure. After recrystallizing the crude product from ethanol under clarifying by activated carbon, the title product is obtained in 49.4% yield, m.p. : 137-138 °C.

Analysis:			
Calculated for $C_{22}H_{24}N_2O_2$			
	C 75.83;	H 6.94;	N 8.04%;
found:	C 76.00;	H 6.97;	N 8.15%.

Example 8

1-oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride

10.7 g of 1-oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-3,8-diazaspiro[4,5]decane (prepared using the process described in Preparation 5 using the appropriate starting material from Preparation 4(a)) are refluxed with 13.2 g of 2-(4-chlorophenyl)ethyl bromide, 8.2 g of anhydrous powdered potassium carbonate and 0.7 g of potassium iodide in 110 ml of methyl isobutyl ketone under nitrogen while stirring for 6 hours. After evaporating the solvent under reduced pressure and adding water to the residue, the mixture is extracted with benzene. The combined benzene solution is washed with water to neutral, dried over anhydrous sodium sulfate, then the benzene solution is filtered through an aluminum oxide layer and evaporated under reduced pressure. After recrystallization of the residue from hexane, the base is

converted to the hydrochloride by adding hydrogen chloride in diisopropyl ether solution. Thus, the title hydrochloride is obtained in 58.4% yield with a decomposition point of 310-315 °C.

Analysis of the base:				
Calculated for $C_{22}H_{31}ClN_2O_3$				
	C 63.93;	H 7.68;	Cl 8.71;	N 6.88%;
found:	C 65.10;	H 7.53;	Cl 8.60;	N 7.00%.

Using the appropriate starting materials the following compounds may be prepared in an analogous manner to the processes described in Examples 1 to 3 or 8.

1-Oxa-2-oxo-3-methyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 119-120 °C;

1-Oxa-2-oxo-4-methylene-3-phenyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 134-135 °C;

1-Oxa-2-oxo-3-ethyl-4-methylene-8-[2-(4-methylphenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 280-282 °C;

1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 125-126 °C;

1-Oxa-2-oxo-4-methylene-3-phenyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p. : 145-147 °C;

1-Oxa-2-oxo-3-ethyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p. : 121-122 °C;

1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p. : 90-92 °C;

1-Oxa-2-oxo-3-isopropyl-4-methylene-8[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p.: 118-119 °C;

1-Oxa-2-oxo-3-methyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p. : 90-91 °C;

1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-(2-phenylethyl) -3,8-diazaspiro[4,5]decane, m.p. : 106-107 °C;

1-Oxa-2-oxo-3-isopropyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 101-102 °C;

1-Oxa-2-oxo-3-methyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 74-75 °C;

1-Oxa-2-oxo-3-ethyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p.: 111-112 °C;

1-Oxa-2-oxo-3-isopropyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 103-104 °C;

1-Oxa-2-oxo-4-methylene-3-phenyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p.: 125-126 °C;

1-Oxa-2-oxo-4-methylene-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 78-79 °C;

1-Oxa-2-oxo-3-[2-(3,4-dimethoxyphenyl)ethyl]-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 114-115 °C;

1-Oxa-2-oxo-3-benzyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p. : 81-82 °C;

1-Oxa-2-oxo-3-decyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrogen maleate, m.p. : 106-107 °C;

1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p.: 121-122 °C;

1-Oxa-2-oxo-3-butyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5/decane, m.p. : 70-71 °C;

1-Oxa-2-oxo-3-methyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p. : 118-119 °C;

1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 104-105 °C;

1-Oxa-2-oxo-3-ethyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 83-84 °C;

1-Oxa-2-oxo-3-methyl-4-methylene-8-[2-(3,4-dimethoxyphenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, m.p.: 278-280 °C; and

1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 93-94 °C.

Example 9

1-oxa-2-oxo-4-methylene-3-(1-naphthyl)-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane

9.9g of 4-ethynyl-4-hydroxy-1-[2-(4-fluorophenyl)ethyl]piperidine are heated with 7.0 ml of 1-naphthyl isocyanate under argon. A violent exothermic reaction occurs. The temperature is maintained between 170 °C and 180 °C by external cooling for one hour. After cooling down and dissolving the solid residue in chloroform, the solution is filtered through an aluminum oxide layer and the filtrate is evaporated under reduced pressure. After recrystallizing the residue from ethanol the title compound is obtained in 65% yield, m.p.: 160-161 °C.

Analysis:				
Calculated for $C_{26}H_{25}FN_2O_2$				
	C 74.98;	H 6.05;	F 4.56;	N 6.73%;
found:	C 75.10;	H 6.25;	F 4.37;	N 6.55%.

Example 10

1-oxa-2-oxo-3-n-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane

3.3 g of n-butyl isocyanate dissolved in 11 ml of benzene are added portionwise to a gently boiling suspension containing 11 g of 4-ethynyl-4-hydroxy-1-[4,4-bis(4-fluorophenyl)butyl]piperidine and 0.09 g of sodium methoxide in 45 ml of benzene under argon while stirring, then the mixture is refluxed for additional 3 to 4 hours. After cooling down the benzene solution is washed with water, dried over anhydrous sodium sulfate, filtered and the solvent is distilled off under reduced pressure. After recrystallizing the residue from diisopropyl ether the title compound is obtained in 79,5% yield, m.p.: 94-95 °C

Analysis				
Calculated for $C_{28}H_{34}F_2N_2O_2$				
	C 71.77;	H 7.31;	F 8.11;	N 5.98%;
found:	C 71.98;	H 7.40;	F 8.24;	N 6.13%.

Example 11

1-oxa-2-oxo-3-butyl-4-methylene-8-[2-(4chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane

13.2 g of 4-ethynyl-4-hydroxy-1-[2-(4-chlorophenyl)ethyl]piperidine are refluxed with 6.5 g of n-butyl isocyanate in 40 ml of 2-picoline in the presence of 0.2 g of anhydrous potassium acetate under argon for 6 hours. After evaporating the solvent under reduced pressure and dissolving the residue in benzene, the organic phase is washed with water and dried over anhydrous sodium sulfate. The benzene solution is filtered through an aluminum oxide layer and evaporated under reduced pressure. After recrystallizing the crude product from hexane the title compound is obtained in 74.5% yield, m.p.: 86-87 °C.

Analysis:				
Calculated for $C_{20}H_{27}ClN_2O_2$				
	C 66.19;	H 7.50;	Cl 9.77;	N 7.72%;
found:	C 66.23;	H 7.57;	Cl 9.90;	N 7.64%.

The following compounds may be prepared in an analogous manner according to the processes described in Examples 9, 10 or 11, using the appropriate starting materials.

1-Oxa-2-oxo-4-methylene-3-propyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 82-83 °C;
1-Oxa-2-oxo-3-ethyl-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p. : 106-107 °C;
1-Oxa-2-oxo-4-methylene-3-(1-naphthyl)-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p. : 127-128 °C;
1-Oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p. : 90-92 °C;
1-Oxa-2-oxo-3-heptyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrogen maleate, m.p.: 121-122 °C;
1-Oxa-2-oxo-3-(3,4-dichlorophenyl)-4-methylene-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 292-295 °C;
1-Oxa-2-oxo-3-cyclohexyl-4-methylene-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 152-153 °C;
1-Oxa-2-oxo-4-methylene-3-propyl-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane, m.p.: 97-98 °C; and
1-Oxa-2-oxo-3-butyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 91-92 °C.

Example 12

1-oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride

3 ml of butylamine dissolved in 3 ml of benzene are dropped to a solution of 8.3 g of 1,3-dioxa-2-oxo-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl]-8-azaspiro [4,5]decane in 17 ml of anhydrous benzene under stirring. Meanwhile the temperature of the reaction mixture raises to 38 - 45 °C. Thereafter the reaction mixture is stirred at room temperature for additional 16 hours, then evaporated under reduced pressure. After take up of the residue in anhydrous ether the title hydrochloride salt is precipitated by adding ethereal hydrogen chloride solution. The title salt is obtained in 87% yield, m.p.: 218-221 °C.

The base is obtained from the hydrochloride by adding ammonium hydroxide solution.

Analysis of the base:				
Calculated for $C_{28}H_{36}F_2N_2O_3$				
	C 69.11;	H 7.46;	F 7.81;	N 9.86%;
found:	C 69.20;	H 7.50;	F 7.64;	N 9.72%.

Example 13

1-oxa-2-oxo-3-methyl-4-methylene-8,8-bis(3-phenylpropyl)-3,8-diazaspiro[4,5]decan-8-ium iodide

6.0 g of 1-oxa-2-oxo-3-methyl-4-methylene-8-(3-phenylpropyl)-3,8-diazaspiro[4,5]decane are refluxed with 5.4 g of 3-phenylpropyl iodide in 60 ml of methyl isobutyl ketone under nitrogen for 4 hours, then the solvent is distilled off under reduced pressure. After adding hexane to the residue the solid precipitate is filtered and recrystallized from ethanol to give the title compound in 86% yield, m.p.: 219-220 °C.

Example 14

1,3-dioxa-2-oxo-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl] -8-azaspiro[4,5]decane hydrogen maleate

A solution of 16.0 g of 1-[4,4-bis(4-fluorophenyl)butyl]-4-butyl-carbamoyloxy-4-ethynylpiperidine in 90 ml of anhydrous dioxane is saturated by dry gaseous hydrogen chloride at 15 to 20 °C, then the reaction mixture is left to stand overnight. The solvent is evaporated at 40 to 50 °C under reduced pressure. After adding water to the residue, the base is liberated with sodium hydrogen carbonate and extracted into benzene. The benzene solution is dried over anhydrous magnesium sulfate, then the solvent is evaporated under reduced pressure. After dissolving the residue in ethyl acetate, the solution is filtered through a silica gel column and the solution thus obtained is evaporated under reduced pressure. After taking up the residue in acetone, the title hydrogen maleate salt is precipitated by maleic acid. The title salt is obtained in 55% yield, m.p.: 149-150 °C.

Analysis for the base:				
Calculated for $C_{24}H_{25}F_2NO_3$				
	C 69.72;	H 6.09;	F 9.19;	N 3.39%;
found:	C 69.85;	H 6.17;	F 9.35;	N 3.12%.

Example 15

1-oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-(2-phenylethyl)-3,8-diazaspiro[4,5]decane

A solution containing 9.1 g of 4-acetyl-4-methylcarbamoyloxyl-1-(2-phenylethyl)piperidine and 0.5 g sodium methoxide in 100 ml of methanol is refluxed under argon for 4 to 5 hours. After cooling down the sodium methoxide is decomposed by adding aqueous ammonium chloride solution, the mixture is diluted with water and methanol is distilled off under reduced pressure. After filtration the precipitate obtained is recrystallized from ethanol to give the title product in 72.1% yield, m.p. : 184-185 °C.

Analysis:			
Calculated for $C_{17}H_{24}N_2O_3$			
	C 67.08;	H 7.95;	N 9.20%;
found:	C 67.11;	H 7.90;	N 9.03%.

Example 16

1-oxa-2-oxo-3-benzyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride

A solution of 6.1 g of 1-oxa-2-oxo-3-benzyl-4-methylene-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]-decane in 120 ml of 0.2 molar hydrochloric acid is refluxed for 10 minutes and then evaporated to a volume of 70 ml under reduced pressure. The mixture is cooled at 1 to 5 °C for 30 minutes, then the crystalline precipitate is filtered and dried to give the title hydrochloride in 98% yield, decomp. at 295 °C.

The base is liberated from the hydrochloride by adding aqueous ammonium hydroxide solution.

Analysis for the base:				
Calculated for $C_{23}H_{27}FN_2O_3$				
	C 69.32;	H 6.83;	F 4.77;	N 7.03%;
found:	C 69.40;	H 6.64;	F 4.85;	N 7.16%.

The following compounds may be prepared in an analogous manner using the processes described in Examples 12 or 16 and using the appropriate starting materials:

1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 197-198 °C;

1-Oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 189-190 °C; 1-Oxa-2-oxo-3-tert-butyl-4-hydroxy-4-methyl-8-[2-(4-fluoro-phenyl)ethyl]-3,8-diazaspiro[4,5]-decane hydrochloride, decomp. at 286-288 °C;

1-Oxa-2-oxo-3,4-dimethyl-4-hydroxy-8[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 220-223 °C;

1-Oxa-2-oxo-3-benzyl-4-hydroxy-4-methyl-8-[4,4-bis (4-fluorophenyl)butyl]-3,8-diazaspiro/4,5]decane hydrochloride, decomp. at 177-179 °C;

1-Oxa-2-oxo-4-hydroxy-3-isopropyl-4-methyl-8-[4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 157-158 °C;

1-Oxa- 2-oxo-4-hydroxy-4-methyl-3-phenyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 274-276 °C;

1-Oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[2-4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p. : 155-156 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 248 °C; the base melts at 138-139 °C;

1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 235 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-(1-naphthyl)-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp, at 180-182 °C;

1-Oxa-2-oxo-3-heptyl-4-hydroxy-4-methyl-8-[4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane, m.p.: 128-129 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-(1-naphthyl)-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 288-290 °C;

1-Oxa-2-oxo-3-ethyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane, m.p.: 139-140 °C;

1-Oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 258 260 °C;

1-Oxa-2-oxo-4-hydroxy-3-isopropyl-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp, at 251-253 °C;

1-Oxa-2-oxo-3-butyl-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 218-220 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 134-136 °C;

1-Oxa-2-oxo-4-hydroxy-4-methyl-3-phenyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro[4,5]decane hydrochloride, decomp. at 346-350 °C;

1-Oxa-2-oxo-3-(3,4-dichlorobenzyl)-4-hydroxy-4-methyl-8-[2-(4-chlorophenyl)ethyl]-3,8-diazaspiro[4,5]-decane hydrochloride, decomp. at 310-315 °C; and

1-Oxa-2-oxo-4-hydroxy-4-methyl-8-[4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro[4,5]decane hydrochloride, m.p.: 130-132 °C.

Non-limiting Examples of pharmaceutical compositions that may be prepared using the compounds according to the present invention include:

a) Preparation of tablets

50.0 g of active ingredient are mixed together with 92 g of lactose, 40 g of potato starch, 4 g of polyvinylpyrrolidone, 6 g of talc, 1 g of magnesium stearate, 1 g of colloidal silicon dioxide (Aerosil) and 6 g

of ultraamylopectin and, after wet granulation, the product obtained is compressed into tablets containing 50 mg of the active ingredient each;

b) Preparation of dragées

The tablets prepared as described above are covered in a manner known per se with a coating consisting of sugar and talc. The dragées are polished by using a mixture of bees wax and carnaube wax. Each dragee weighes 250 mg;

c) Preparation of capsules

100 mg of active ingredient, 30 g of sodium lauryl sulfate, 280 g of starch, 280 g of lactose, 4 g of colloidal silicon dioxide (Aerosil) and 6 g of magnesium stearate are thoroughly mixed together and after sieving, the mixture obtained is filled into hard gelatine capsules containing 20 mg of the active ingredient each ;

d) Preparation of suppositories

30.0 mg of active ingredient are thoroughly mixed with 60.0 mg of lactose. Simultaneously, 1910.0 mg of suppository base (e.g. Witepsol 4) are made molten (all weights are calculated for one suppository), cooled to 35 °C and the mixture of the active ingredient and lactose are mixed thereinto using a homogenizer. The product obtained is poured into cooled conic moulds. Each suppository weighes 2000 mg.

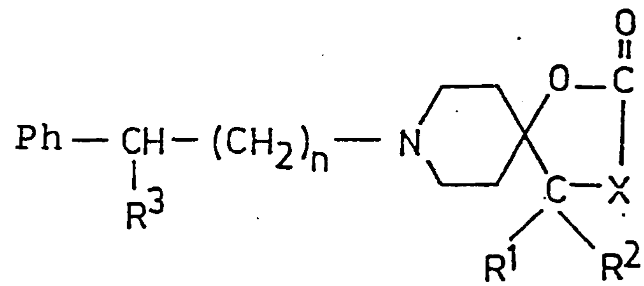
e) Preparation of a suspension

Components in 100 ml of the suspension:	
Active ingredient	1.00 g
Sodium hydroxide	0.26 g
Citric acid	0.30 g
Nipagin (methyl 4-hydroxybenzoate sodium salt)	0.10 g
Carbopol 940 (polyacrylic acid)	0.30 g
96% Ethanol	1.00 g
Raspberry flavour	0.60 g
Sorbitol (aqueous solution of 70%)	71.00 g
Distilled water for injection purpose up to	100.00 ml

After adding carbopol in little portions to the solution of nipagin and citric acid in 20 ml of distilled water under vigorous stirring, the solution obtained is left to stand for 10 to 12 hours. Subsequently, the amount given above of sodium hydroxide dissolved in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic solution of the raspberry flavour are dropped in under stirring. The active ingredient is added in small portions to this mixture and suspended by using a submerged homogenizer. Finally, the suspension is supplemented to 100 ml by adding sufficient distilled water and the syrupy suspension is led through a colloid mill.

Claims

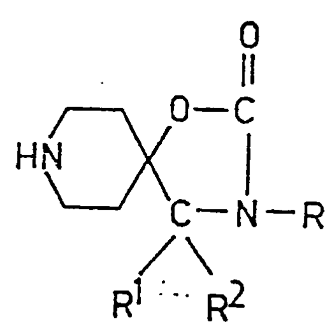
1. A compound of formula (I),



(I)

wherein
X represents an oxygen atom or an NR group, wherein
R represents a hydrogen atom or a C_{1-12} alkyl or C_{3-6} cycloalkyl group, or a carbocyclic C_{6-10} aryl or carbocyclic C_{6-10} aryl-C_{1-14} alkyl group optionally substituted on the aromatic ring by one or more halogen atoms, C_{1-4} alkyl or C_{1-4} alkoxy groups;
R^1 and R^2 together represent a methylene group or, when X is a NR group, one of R^1 and R^2 additionally represent a hydroxyl group and the other additionally represents a methyl group;
R^3 represents a hydrogen atom or a phenyl group optionally substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxyl group;
Ph represents a phenyl group unsubstituted or substituted by one or more halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl or trihalomethyl groups; and
n is 1, 2, 3;
and optical isomers and mixtures thereof and all acid addition and quaternary ammonium salts thereof.
2. A compound of formula (I) as defined in Claim 1 selected from the group comprising:
1-oxa-2-oxo-3-tert-butyl-4-methylene-8-[4,4-bis(4-fluorophenyl)butyl-3,8-diazaspiro [4,5] decane,
1-oxa-2-oxo-3-cyclohexyl-4-methylene-8-[,4, 4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro [4,5] decane,
1-oxa-2-oxo-3-butyl-4-hydroxy-methyl-8 [4,4-bis(4-fluorophenyl)butyl]-3,8-diazaspiro [4,5] decane,
1-oxa-2-oxo-4-methylene-3-phenyl-8 [4,4-bis(4-fluorophenyl)- butyl]-3,8-diazaspiro [4,5] decane,
1-oxa-2-oxo-4-hydroxy-4-methyl-3-propyl-8-[2-(4-fluorophenyl)ethyl]-3-8-diazaspiro [4,5] decane,
1,3-dioxa-2-oxo-4-methylene-8-[4,4-bis (4-fluorophenyl)-butyl]-8-azaspiro [4,5] decane,
1-oxa-2-oxo-3-cyclohexyl-4-hydroxy-4-methyl-8-[2-(4-fluorophenyl)ethyl]-3,8-diazaspiro [4,5] decane and 1-oxa-2-oxo-3-ethyl4-hydroxy-4-methyl-8- [2-(4-fluorophenyl)-ethyl]-3,8-diazaspiro [4,5] decane
and all optical isomers and mixtures thereof and acid addition and quaternary ammonium salts thereof.
3. A pharmaceutical composition which comprises a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof in admixture with a pharmaceutically acceptable carrier and/or additive.
4. A process for the preparation of a compound of formula (I) as defined in Claim 1 which comprises

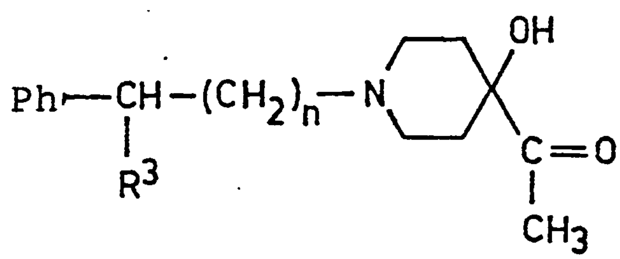
a) for the preparation of compounds of formula (I) wherein X is a group NR, reacting a 2-oxo-3,8-diazaspiro[4,5]decane derivative of formula (II),



(II)

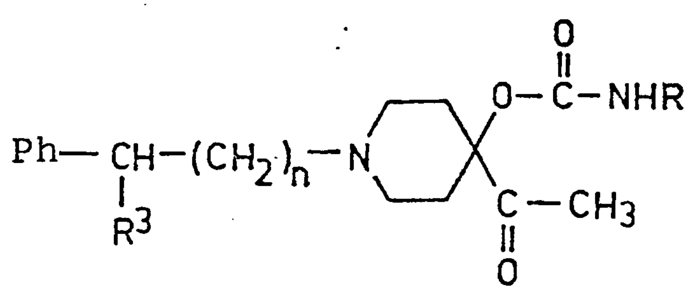
wherein R, R^1 and R^2 are as defined in claim 1, with a phenylalkane derivative of formula (III),

d) for the preparation of compounds of formula (I) as defined in process (b) (β) above, cyclizing in the presence of a base a 4-carbamoyloxy-4-ethynylpiperidine derivative of formula (V) as defined above;
or
e) for the preparation of a compound of formula (I) wherein is X is a group NR and one of R_1 and R_2 is a hydroxy group and the other is a methyl group, reacting a 4-acetyl-4-hydroxypipridine derivative of formula (VII),



(VII)

wherein R^3, Ph and n are as defined above, with an isocyanate of formula R-NCO, wherein R is as defined above, and cyclizing the thus formed compound of formula (VIII)



(VIII)

wherein R, R^3 Ph and n are as defined above;
or
f) for the preparation of compounds of formula (I) as defined for process (e) above, cyclizing a 4-acetyl-4-carbamoyloxypiperidine derivative of formula (VIII) as defined above;
followed if desired or necessary,
by reacting a compound of formula (I) as prepared above wherein X is an oxygen atom and R^1 and R^2 together are a methylene group with an amine of formula $R\text{-}NH_2$ wherein R is as defined above in order to prepare a compound of the formula (I) wherein X is a group NR and one of R^1 and R^2 is a hydroxyl group and the other is a methyl group,
and/or if desired or necessary,
transforming a compound of the formula (I) as prepared above into another compound of the formula (I) as defined in Claim 1,
and/or desired or necessary,
reacting a compound of formula (I) as prepared above with an acid to obtain the acid addition salt thereof and/or treating a salt of a compound of the formula (I) as prepared above with a base to liberate the base form thereof and /or converting a thus prepared compound of the formula (I) into its quaternary ammonium salt.

5. A process as claimed in claim 4 process a) wherein Y is either a chlorine or bromine atom or a p-toluenesulphonyloxy group.

6. A process as claimed in claim 4 process (b) (β) wherein the reaction is carried out as a single step without separating the compound of formula (V).

7. A process as claimed in claim 4 process e) which comprises carrying out the reaction in the presence of triethylamine at the boiling point of the reaction mixture.

8. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of hypoxic brain damage in mammals.

9. The use of a compound of formula (I) as defined in claim 1 for the manufacture of a medicament for use in inhibiting calcium-uptake in mammals.

10. A process for the preparation of a pharmaceutical composition as defined in Claim 3 which comprises admixing a compound of formula (I) or a pharmaceutically acceptable acid addition or quaternary ammonium salt thereof as defined in Claim 1 with a pharmaceutically acceptable carrier and/or additive.